The Invention

As indicated in the Background of the Invention, due to the widely varied clinical applications for IGF-I, compositions with desirable characteristics are in great demand, and several IGF-I formulations have been made. See, e.g., U.S. Patent No. 5,126,324. In particular, compositions with high concentrations of IGF-I are preferable for certain indications. Additionally, it is preferable to administer IGF-I compositions at physiological pHs. It is also preferable that the IGF-I in such compositions remains soluble and that the compositions are capable of storage for extended periods of time at refrigerated temperatures.

Physical parameters such as temperature and pH affect the solubility of IGF-I. For example, below about pH 5.0, IGF-I is soluble at concentrations of about 80-100 mg/ml while above pH 5.5 the solubility drops about ten-fold. Additionally, IGF-I is less soluble at lower temperatures. Thus, in order to provide IGF-I compositions capable of refrigerated storage, e.g., to retain stability, while still maintaining acceptable IGF-I solubility levels, compositions are now generally formulated at a non-physiological pH of less than 5.0. Unfortunately, administration of IGF-I compositions having a non-physiological pH causes pain and irritation at the site of injection.

The present invention provides for IGF-I compositions in which IGF-I is highly soluble at pHs of 5.5 or greater and highly soluble when the composition is stored at 4°C. These compositions have soluble IGF-I present at higher concentrations and at higher pHs than previously possible.

The Rejection of the Claims Under 35 USC §112, First Paragraph, Should Be Withdrawn

Claims 29-48 and 85-112 were rejected under 35 USC §112, first paragraph. This rejection is respectfully traversed.

The Examiner indicates that the specification is enabled for a composition comprising biologically active insulin-like growth factor-1 (IGF-I) at a concentration of 12 mg/ml to 200 mg/ml and at a temperature of 4°C, a solubilizing compound of arginine, acetyl-arginine, or guanidine hydrochloride, and a buffer of pH 6.0. The

Examiner however indicates that the specification lacks sufficient enablement for the breadth of the pending claims.

The present specification clearly enables claims 29-48 and 85-98. To be enabling under 35 USC §112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. Furthermore, the test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *Johns Hopkins University v. Cellpro, Inc.*, 152F.3d 1342, 1360 (Fed. Cir. 1998).

The pending claims recite biologically active IGF-I or a biologically active IGF-I analogue having at least 70% sequence identity with human IGF-I. IGF-I analogues are defined in the specification at page 5, lines 27-28. Furthermore, page 6 describes IGF-I analogues having 70% sequence identity. The specification provides several routine bioassays for testing activity of IGF-I analogues at page 5, line 29, through line 5 of page 6. Further guidance as to IGF-I analogue candidates is provided at page 5, lines 29-30, and at page 6, line 7, through line 18 of page 7.

Given this disclosure, one of skill in the art could readily make analogues of IGF-I, test for their biological activity, use the methods of the invention, and readily determine, without undue experimentation, whether the composition comprising an IGF-I analogue and a solubilizing agent, as defined in the disclosure, constitutes the claimed IGF-I composition. It is clearly stated that the composition, at a temperature of about 4°C and a pH of at least about 5.5, will have IGF-I or its analogue "at a concentration of about 12 mg/ml or higher" and that the IGF-I analogue "will retain IGF-I activity and/or the ability to bind IGF-I receptors". See page 5, lines 27-28, and page 10, lines 20-26. As noted above, methods for determining IGF-I activity are well known in the art, and specific examples are disclosed in the specification at page 5, line 34, through line 6 of page 6. Likewise, for IGF-I or any one of its possible analogues, one of skill in the art

could readily determine whether a dipeptide containing one or more arginine residues, a tripeptide containing one or more arginine residues, or another solubilizing compound comprising a guanidinium group would retain the activity of increasing solubility of IGF-I at a pH of about 5.5 or greater and at a temperature of about 4°C such that the claimed IGF-I composition has an IGF-I concentration of at least about 12 mg/ml under these pH and temperature conditions. Suitable solubilizing compounds are described and examples provided on pages 10-11 of the specification. Again, the specification provides sufficient disclosure for one of skill in the art to use other solubilizing compounds.

The Examiner indicates that "it is necessary to have more guidance regarding the sequences of IGF-I analogs and structures of arginine analogs, and to carry out further experimentation." Official Action mailed October 9, 2001, at page 5. However, as noted above, such IGF-I analogues and amino acid analogues of arginine are described in the specification, and are also well known in the art. Applicants have demonstrated that compositions having a pH of about 5.5 or greater and high concentrations of soluble IGF-I at 4°C can be prepared when formulated with a solubilizing compound comprising a guanidinium group. Such compositions were not possible prior to Applicants' invention. Having demonstrated this possibility for IGF-I, it is clearly within the skill of the art to use IGF-I analogues and arginine analogues to prepare other IGF-I compositions that meet the limitations set forth in these claims. Further, those skilled in the art following the teachings of Applicants' disclosure would know how to test, without undue experimentation, for the operability of other embodiments encompassed by these claims. Accordingly, the enablement requirement of 35 USC §112, first paragraph, has been met.

Despite the breadth of Applicants' disclosure, the Examiner asserts that the specification is only enabling for the working examples set forth therein. However, Applicants respectfully note that it is improper to limit the scope of Applicants' claimed invention to that which is disclosed in working examples. See *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973), where the court held "we do not regard section 112, first

paragraph, as requiring a specific example of everything *within the scope* of a broad claim. . . . What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. This it may not do."

The Examiner further argues that "the expectation of success is unpredictable." Office Action mailed October 9, 2001, at page 5. However, the Examiner provides no support for this statement. Prior to the present invention one could not have predicted that the claimed compositions would have been possible. Applicants have clearly demonstrated the impact of solubilizing compounds comprising a guanidinium group on IGF-I solubility in compositions that are formulated at pHs greater than 5.5 and stored at 4°C. Applicants have asserted that the compositions of the invention can be prepared using IGF-I analogues and other solubilizing compounds having a guanidinium group, including arginine analogues. Now that Applicants have demonstrated compositions comprising biologically active IGF-I at higher pHs and which maintain the IGF-I in its soluble, biologically active state when stored at 4°C, one of skill in the art can readily produce other IGF-I compositions having similar IGF-I solubility characteristics based on the guidance provided in the specification.

In citing to the unpredictability of Applicants' invention as a basis for the enablement rejection, the Examiner is questioning the truth of Applicants' assertions. Yet no evidence has been provided in support of the Examiner's position. Applicants respectfully request that the Examiner provide specific evidence under 37 CFR §1.107(b) to support the Examiner's position. Without citation of this specific evidence, the rejection of the claims under 35 USC §112, first paragraph, should be withdrawn.

The Rejections of the Claims Under 35 USC §112, Second Paragraph, Should Be Withdrawn

Claims 29-48 and 85-112 were rejected under 35 USC §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The Examiner has objected to the use of the term "at least about." Applicants assert that the term is definite. Words such as "about" are often used in claims to prevent a potential infringer from avoiding literal infringement by making minor modifications. Likewise, the use of "at least" is definite and does not of itself justify a rejection for indefiniteness under 35 USC §112. See, *In re Fisher*, 166 USPQ 18, 23 (C.C.P.A. 1970).

Claims 29-48 were rejected for use of the term "biologically active analogue" or "IGF-I or analogue." The Examiner indicates it is unclear what sequence the IGF-I analogue has. In contrast to the Examiner's statement, it is indicated in the claim that the analogue shares at least 70% sequence identity with the amino acid sequence for human IGF-I. One of skill in the art could prepare analogues and readily determine whether an analogue fell within the scope of the claim. The Examiner is further directed to page 6 of the specification, which defines "sequence identity" and provides methods for determining sequence identity.

Claims 29-45, 85-98 and 101-112 were rejected as indefinite for the use of the term "in an amount sufficient to make IGF-I or analogue thereof soluble." The Examiner indicates that the phrase renders the claim indefinite as it is unclear what amount of solubilizing compound is needed. As indicated previously, the present invention is based on the discovery that guanidinium-containing compounds are able to enhance the solubility of IGF-I above pH 5.5, providing for stable IGF-I compositions with higher concentrations than previously possible. Page 11 of the specification indicates that the concentration of the solubilizing compound will affect the achievable concentration of the IGF-I. However, it is noted that the concentration of IGF-I and the temperature will affect the solubility of the IGF-I. Accordingly, "the amount of solubilizing compound present will depend on the nature of the guanidinium group compound, its solubility, its affect on solubility of IGF-I, the desired concentration of IGF-I to be achieved in the composition, and the temperature at which the composition will be maintained. The

optimum concentration for each solubilizing compound may differ but is readily determined by one of skill in the art." Specification, page 11, lines 12-17. The specification on the same page further indicates that the solubilizing compound will be present in the composition from about 10 mM to about 1 M. Accordingly, it is asserted that the phrase "in an amount sufficient to make IGF-I soluble" is definite, and the rejection should be withdrawn.

Claims 31 and 46-48 were rejected as indefinite for the use of the term "arginine analogue." As noted above, the solubilizing compound of the invention comprises a guanidinium group to enhance the solubility of the IGF-I compound. Claims 31 and 46 have been amended to clarify this aspect of the invention. Accordingly, claim 31 recites a solubilizing compound that is selected from the group consisting of arginine, N-acetyl-arginine, a dipeptide containing arginine, and a tripeptide containing arginine. Claim 46 recites a solubilizing compound that is selected from the group consisting of arginine, N-acetyl-arginine, a dipeptide containing arginine, a tripeptide containing arginine, and guanidine hydrochloride. The dipeptide and tripeptide included in these compositions must increase solubility of IGF-I or analogue thereof at a pH of at least about 5.5 such that the claimed IGF-I compositions have an IGF-I concentration of at least about 12 mg/ml under the recited pH and temperature conditions. Applicants respectfully submit that these claims are definite, and the rejection should be withdrawn.

Claims 31 and 46-48 were rejected for the use of the term "a pH of about 5.5 or greater." While Applicants assert that even one unskilled in the art would know what is meant by "about 5.5 or greater" the claims have been amended to set forth "at a pH of at least about 5.5." As indicated above, the courts have held that the terms "about" and "at least" are definite.

Claims 33 and 47 were rejected as indefinite for the use of the term "at least 95% sequence identity." As noted above, one of skill in the art can readily determine a sequence having at least 95% sequence identity to IGF-I. Furthermore, as noted above, page 6 of the specification defines "sequence identity" and provides methods for determining sequence identity. Accordingly, the phrase is not indefinite, and the rejection should be withdrawn.

Claims 35-39, 88-92, and 102-106 were rejected as indefinite for the use of the term "from about . . . to about . . . ". The Examiner indicates use of the term "between . . . to . . . " or "about . . . to about . . . " would be acceptable. Applicants assert that the phrase "from about . . . to about . . . " is essentially the same as suggested by the Examiner. Accordingly, it is believed that the claims are definite, and the rejection should be withdrawn. Should the Examiner maintain the rejection, further explanation is required as the Examiner suggested amendments mirror the claims as they are presently written.

For these reasons, the rejections of the claims under 35 USC §112, second paragraph, should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 USC §112, first and second paragraphs, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper.

However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR

§1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Version with Markings to Show Changes Made:

Please amend claims 31 and 46 to read as follows:

31. (Once amended) The composition of claim 29, wherein said solubilizing compound is selected from the group consisting of arginine[or an arginine analogue], N-acetyl-arginine, a dipeptide containing arginine, and a tripeptide containing arginine, wherein said [arginine analogue is an amino acid analogue of arginine that]dipeptide or said tripeptide increases solubility of said IGF-I or analogue thereof at a pH of at least about 5.5 [or greater].

46. (Once amended) A composition comprising:

(a) biologically active insulin-like growth factor-1 (IGF-I) or biologically active analogue thereof having an amino acid sequence that shares at least 70% sequence identity with the amino acid sequence for human IGF-I, wherein said IGF-I or analogue thereof is present at a concentration of at least about 12 mg/ml when said composition is at a temperature of about 4°C;

(b) a solubilizing compound selected from the group consisting of arginine[, an arginine analogue], N-acetyl-arginine, a dipeptide containing arginine, a tripeptide containing arginine, and guanidine hydrochloride, wherein said [arginine analogue is an amino acid analogue of arginine that]dipeptide or said tripeptide increases solubility of said IGF-I or analogue thereof at a pH of at least about 5.5 [or greater]; and

(c) a buffer such that the composition has a pH of about pH 5.5 to about pH 9.0.

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